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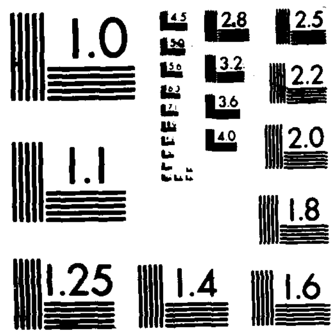

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LABORATORY NOTE NO. 87-63

REDUCED HEMORRHAGE TOLERANCE IN HYPERTHERMIC CONSCIOUS PIGS

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LETTERMAN ARMY INSTITUTE OF RESEARCH
PRESIDIO OF SAN FRANCISCO, CALIFORNIA 94129

Reduced hemorrhage tolerance in hyperthermic conscious pigs
--Williams, Bossone, Wade, Hannon

In conducting the research described in this report, the investigation adhered to the "Guide for the Care and Use of Laboratory Animals," as promulgated by the Committee on Revision of the Guide for Laboratory Animal Facilities and Care, Institute of Laboratory Animal Resources, National Research Council.

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ABSTRACT

We evaluated the cardiovascular response to hemorrhage (38.5 ml/kg over 60 min) in conscious normothermic (n=8) and hyperthermic (40.4 ± 0.4°C, mean SEM; n=5) Duroc Swine (18-25 kg); hyperthermia was defined as a rectal temperature exceeding the normal range, (39.7 ±0.1°C; n= 35). Animals were surgically prepared with a carotid artery catheter and splenectomized seven days prior to experiments. Measurements were made at 0, 10, 20, 30, 45, and 60, minutes during hemorrhage and at 15, 30, 60, 120, 180, an 240 minutes after hemorrhage. All eight of the normothermic pigs survived. One of the animals with an elevated temperature died in the course of the hemorrhage and two after hemorrhage($P<0.035$). Before hemorrhage, animals with elevated body temperature had significantly ($P<0.05$) increased mean arterial pressures 119±3 vs 99±3 mmHg) and heart rates (143±7 vs 112±5 b/m) compared to animals with normal body temperatures. At the end of hemorrhage there was no difference in mean arterial pressures (48 ± 11 mmHg, n=4) for hyperthermic pigs and (48 ± 2 mmHg, n=8) for normals. Heart rates at the end of hemorrhage were greater in the hyperthermic (183±26 b/m) than in the normothermic pigs (146±8 b/m). Pigs with elevated body temperature, presumably due to some low grade infection at the catheter exit site, had a reduced tolerance to hemorrhage.

ABSTRACT

We evaluated the cardiovascular response to hemorrhage (38.5 ml/kg over 60 min) in conscious normothermic (n=8) and hyperthermic (40.4 ± 0.4°C, mean SEM; n=5) Duroc Swine (18-25 kg); hyperthermia was defined as a rectal temperature exceeding the normal range, (39.7 ±0.1°C; n=35). Animals were surgically prepared with a carotid artery catheter and splenectomized seven days prior to experiments. Measurements were made at 0, 10, 20, 30, 45, and 60, minutes during hemorrhage and at 15, 30, 60, 120, 180, an 240 minutes after hemorrhage. All eight of the normothermic pigs survived. One of the animals with an elevated temperature died in the course of the hemorrhage and two after hemorrhage ($P<0.035$). Before hemorrhage, animals with elevated body temperature had significantly ($P<0.05$) increased mean arterial pressures (119±3 vs 99±3 mmHg) and heart rates (143±7 vs 112±5 b/m) compared to animals with normal body temperatures. At the end of hemorrhage there was no difference in mean arterial pressures (48 ± 11 mmHg, n=4) for hyperthermic pigs and (48 ± 2 mmHg, n=8) for normals. Heart rates at the end of hemorrhage were greater in the hyperthermic (183±26 b/m) than in the normothermic pigs (146±8 b/m). Pigs with elevated body temperature, presumably due to some low grade infection at the catheter exit site, had a reduced tolerance to hemorrhage.

During the Vietnam era hemorrhagic shock was a major cause of combat fatalities (1). In order to evaluate treatment of hemorrhagic shock in combat casualties a conscious porcine model was developed by Hannon et al (2) at Letterman Army Institute of Research. This model was designed to mimic battlefield exsanguination. It allows us to test therapies in the laboratory and to measure physiological variables. Our observations of this model between time of surgical placement of catheter and hemorrhage revealed that some of the swine were hyperthermic. Catheter sepsis is a problem in chronic instrumentation of animals for experimental purposes and in dogs it has been shown to vary cardiovascular responses to hemorrhage (3). We analyzed cardiovascular responses following hemorrhage in chronically instrumented swine to determine if an elevation in body temperature alters cardiovascular responses. All of the normothermic swine survived; whereas, 3 of the 5 febrile swine died. Because of the fluctuation in physiological values and the limited survival potential, we determined that swine with hyperthermia should be eliminated from physiological studies.

METHODS

The methods described in this section are summarized from the work of Hannon et al (2) at Letterman Army Institute of Research. Thirteen immature Yorkshire pigs were obtained from a commercial breeder (J.C. Boswell; Corcoran, CA). After an overnight fast each pig received a pre-anesthetic intramuscular injection of 2.2 mg/kg xylazine halathane anesthesia induced by face mast and maintained with an endotracheal catheter. A celiotomy was performed and the spleen was removed according to standard techniques with double ligation of all vascular pedicles. The left carotid artery of each pig was exposed and 1.27nm I.D. x 2.03nm O.D. polyvinledine catheter type (S-54 HJ Tygon, Norton Plastic and Synthetic, Akron, OH) was inserted to the level of the aorta and secured by ligatures around the carotid artery. The free end of the catheter was tunneled beneath the skin and exited on the dorsal surface of the neck. The exteriorized portion was fitted with an 17-gauge Intramedic Luer Stub Adapter (Clay Adams, Parsippany, NJ) and capped with an Argyle Intermittent Infusion Plug (Brunswick Co; St Louis, MO). Following wound closure the catheter was filled through the infusion plug with heparin (1000 units/ml). The catheter exit site was protected by a 5cm x 7.5cm hole cut in the patch portion next to the skin to allow catheter access. After a 7 to 10-day recovery period and an overnight fast each pig was brought into a quiet laboratory in a portable cage and given a variety of fabric bedding material. After 15 to 30 minutes of rooting and rearrangment, most animals voluntarily assumed a recumbent position. When so positioned, the intermittent plug was removed and the stub adapter was connected to a 12-inch pressure monitor- injection line (Pharmaseal,

Inc), also filled with heparinized saline. The transducers, suspended by clamps on a ring stand located just outside the portable cage, were height-adjusted to match heart level in the recumbent animal. Transducer output was monitored with a Gould Brush 220 Physiological Recorder. In pilot studies not reported here, cardiovascular function in the conscious pigs was found to vary erratically unless a metabolic steady state had been established and was maintained before baseline measurements were made. Consequently, control values in this study were obtained only after 30 minutes or more of uninterrupted recumbent rest. At the end of the rest period, three sets of measurements made at 10-minute intervals and average control values were calculated. Included in these measurements were heart rate and mean arterial pressures. Immediately after the measurements, the hemorrhage was started. Estimates of 50% blood volume were calculated on the basis of the regression equation for swine reported by von Engelhardt (4): Total Blood Volume/kg=95 (Body Weight in kg)-0.068. The one-hour period of hemorrhage was selected arbitrarily, to simulate a period of hemorrhage such as might be seen in combat casualties. The rate of blood loss was based, again arbitrarily, on an exponential scale such that 10% increments of blood volume were removed over successive intervals of 9, 10, 11.5, 13.5, and 16 minutes. To avoid computational errors in determining total blood volume and the 10 through 50% volume increments, a program developed for Texas Instrument Programmable 59 calculator was used. At the end of each 10% increment of blood volume reduction, the heart rate and arterial pressure measurements were made. Data were obtained and analyzed on pigs during and after hemorrhage to determine the effects of hyperthermia on physiological variables such as heart rate and mean arterial pressure. Values from hyperthermia animals were compared with values from normothermic animals by using a two-way analysis of variance ($P<0.05$). The ultimate results were expressed in terms of survival, i.e. the number of normothermic swine versus hyperthermic swine which survived. Survival rates were compared with the Fisher Exact Test.

RESULTS

There was no significant difference in body weight between normothermic and hyperthermic groups. The blood volume removed in the normothermic group was not significantly different from that removed from the hyperthermic (Table 1). There was a significant difference in survival between the normothermic and hyperthermic groups. Five of the thirteen swine were hyperthermic, three of the five hyperthermic died within two hours after beginning of hemorrhage; whereas, all of the normothermic survived (Fig 1). The hyperthermic swine had elevated heart rates (Fig 2) and mean arterial pressures (Fig 3) throughout the study; however, blood pressures were the same for both normothermic and hyperthermic groups at the end of hemorrhage.

TABLE. CHARACTERISTICS OF THE SWINE

	NORMOTHERMIC n = 8	HYPERTHERMIC (40.4 ± 0.4°C) n = 5
BODY WEIGHT (kg)	22.6 ± 0.7	21.9 ± 0.9
BLOOD VOLUME REMOVED (ml)	871 ± 30	843 ± 32

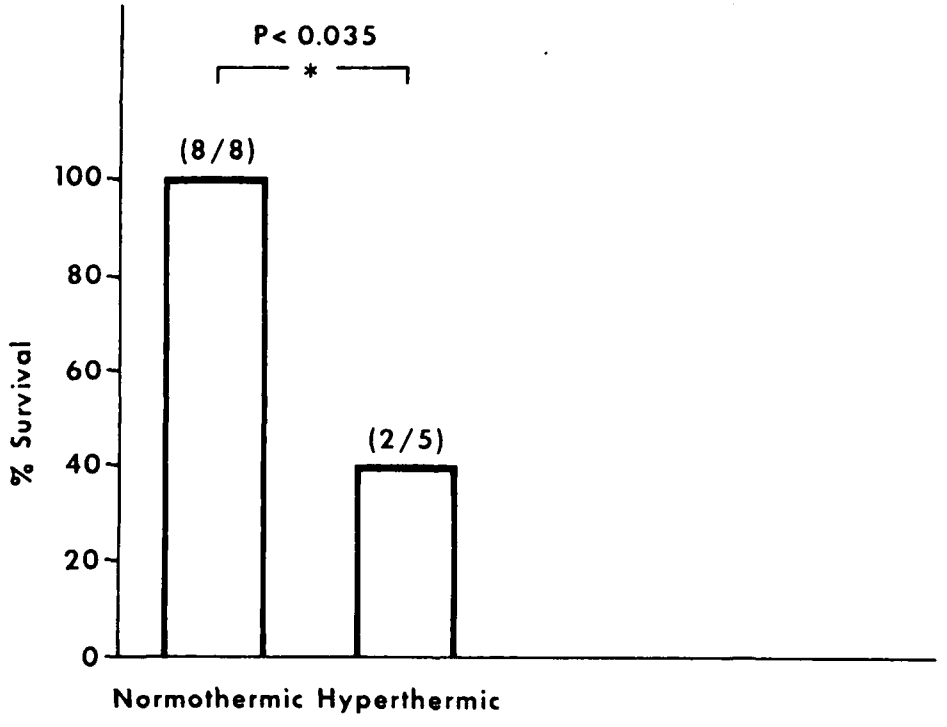
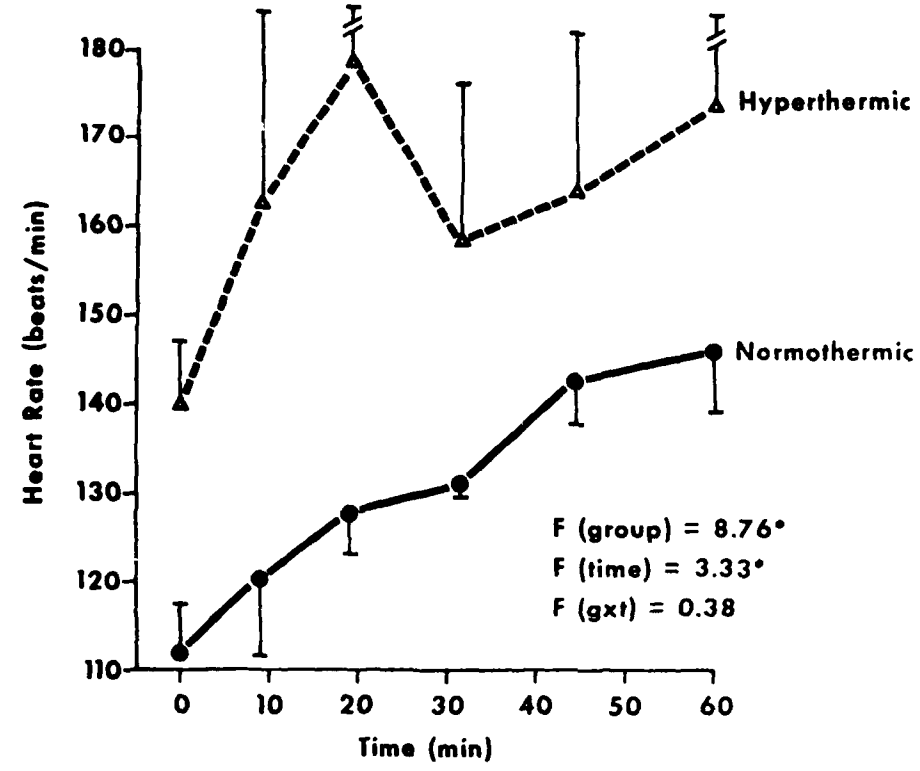


Figure 1. Percentage of survivors from the two treatment groups, normothermic and hyperthermic, of conscious swine submitted to hemorrhage.



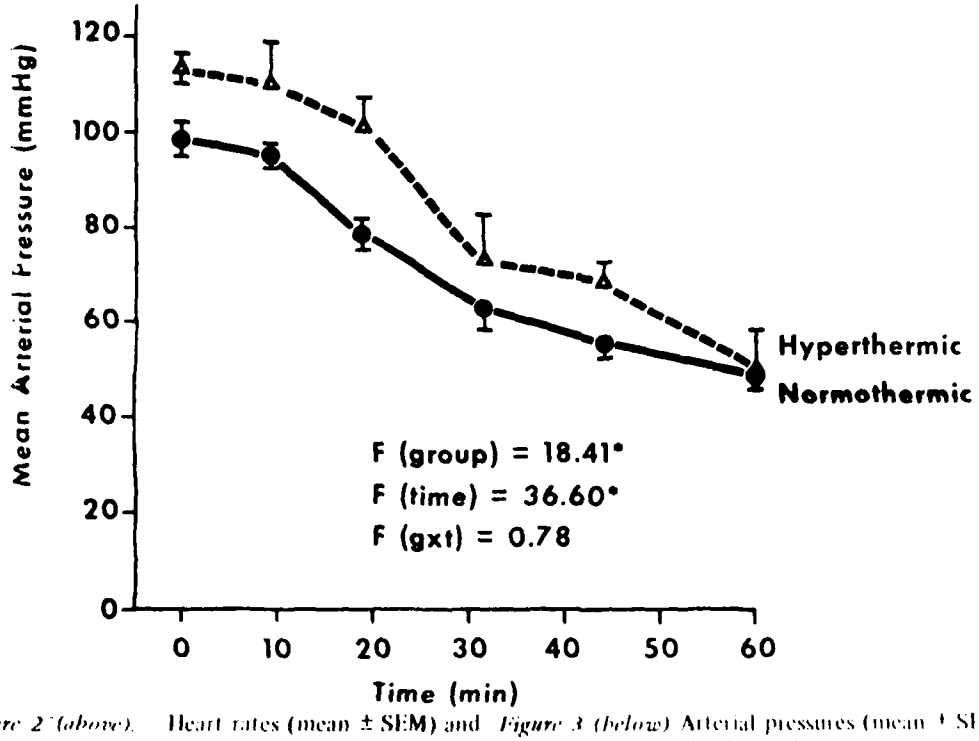


Figure 2 (above). Heart rates (mean ± SEM) and *Figure 3 (below)* Arterial pressures (mean ± SEM) of conscious swine in two treatment groups-one normothermic, the other hyperthermic.

DISCUSSION

In this study the conscious splenectomized swine model with associated hyperthermia had a reduced tolerance to hemorrhage. Results from our study revealed that hyperthermic pigs showed a significant increase in both heart rate and blood pressure. Survival rate was also significantly reduced. Hyperthermia in this study was defined as a rectal temperature exceeding the normal value 39.9 ±0.1°C; determined from our colony of 35 splenectomized pigs. Whereas, the average temperature of swine is 38.8°C and is pathological when it exceeds 39.7°C (5). Various factors, such as low grade infection, iatrogenic fever, excitation, stress, and malignant hyperthermia, could cause hyperthermia. The breed of swine in our study population, Duroc, has a low susceptibility to malignant hyperthermia. Furthermore, we minimized excitation and stress; the pigs were unrestrained, had bedding, and were recumbent at least 30 minutes and often fell asleep before measurements were obtained.

We proposed that our hyperthermic swine had elevated temperatures because of low grade infections introduced by rolling over in their feces in the cages after the implantation of catheters. Blood samples of similiarly surgically prepared swine were submitted for bacterial testing. Bacterial findings were identified as Serratia marceans, Enterobacter cloave, Pseudomonas maltophilia, and a Pseudomonas-like virus (Personal communication by David Brooks, Clinical Investigations at Letterman Army Medical Center).

Wood et al (3) showed that hyperthermia was not unusual in dogs who had implantation of arterial catheters. They attributed hyperthermia to viral infection or iatrogenic fever from wound sepsis. The dogs studied by Wood et al (3) had increased heart rate and decreased blood pressure associated with an elevated temperature, similar, to that observed in swine in the present study.

CONCLUSIONS AND RECOMMENDATIONS

Hyperthermic swine have elevated heart rates and mean arterial pressures compared to normothermic andimals at rest and during hemorrhage. Hyperthermia also decreases the chances for survival during hemorrhage. Swine with low grade hyperthermia should not be included in studies to determine "normal" responses to hemorrhage.

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